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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/642,277	08/18/2000	Seth P. Finklestein	CBA003.01	7436

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FOLEY HOAG, LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BLVD
BOSTON, MA 02110

EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/642,277	FINKLESTEIN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the "Reply" filed 26 December 2002 (Paper No. 19) in reply to the Non-Final Office Action mailed 19 June 2002 (Paper No. 18). Claims 1-48 were considered in Paper No. 18. Claims 13, 14, 15, 17 and 27-29 were amended and claims 3 and 36-48 were canceled in Paper No. 19. Claims 1,2 and 4-35 are pending and under consideration herein.

Response to Amendment

Rejection of claims 3 and 36-48 is rendered moot by the cancellation of the claims in Paper No. 19.

Claim Objections

Objection to claims 13 and 14 is withdrawn in view of the amendments of the claims according to the Examiner's instructions. The claims are newly objected to, however, because the abbreviation for sequence identifier number still does not conform to the accepted format (i.e. SEQ ID NO:; see MPEP 2421.02).

Claim Rejections - 35 USC § 112

Claims 1, 2 and 4-35 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons of record in Paper No. 18 and set forth herein below in the section entitled "Response to Arguments".

Claims 13 and 27 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description for the full scope of the claimed subject matter for reasons of record and set forth herein below in the "Response to Arguments".

Rejection of claims 13 and 27 under 35 U.S.C. § 112, second paragraph, is withdrawn in view of the amendments to the claims in Paper No. 19.

Claim Rejections - 35 USC § 103

Claims 1, 2, 4, 6-20, and 22-35 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Andsberg *et al.* in view of Alp *et al.* and in further view of Ip *et al.* and Daughaday et *al.* for reasons of record and herein below in the "Response to Arguments".

Rejection of claims 5 and 21 under 35 U.S.C. § 103(a) is withdrawn in view of the arguments of record in Paper No. 19.

Response to Arguments

35 U.S.C. § 112, first paragraph, enablement

Claims 1-48 were rejected under 35 U.S.C. §112, first paragraph, on the ground that the "specification... does not reasonably provide enablement for a method of treating a subject with CNS damage... [or] for the use of the method of the invention in treating the various diseases claimed." (Office Action dated 6/19/02, page 3).

Amount of direction provided and existence of working examples:

In response to the examiner's assertion that the specification fails to disclose how long the enhanced recovery in rats lasts, whether it is long enough to see a therapeutic effect, and how to determine the appropriate dosage and other parameter such as the best route of administration, and frequency of administration, Applicant argues, "the length of recovery is irrelevant to the sufficiency of an enabling description. Rather, Applicants note that the enablement analysis concerns whether the disclosure enables a person of ordinary skill in the art to practice the claimed subject matter, not how well the claimed subject matter works. Second, Applicants refer the Examiner to pages 33-34 and Table 2 of the specification for description of dosages, to page 33 for description of routes of administration, and to page 34 for description of dosage frequency" (Paper No. 19, page 10).

These arguments have been fully considered but are not found persuasive. The previous Office Action indicates that the disclosure is enabling for a method of transplanting neural stem cells together with FGF as a neural stimulant wherein the method results in increased integration and differentiation of neural stem cells and ameliorates the effects of ischemic injury in a rat model, which is the subject matter reduced to practice. Further, as the rat model used is an accepted model of ischemic injury in mammals, the method is enabled for amelioration of the effects of ischemic injury in mammals. However, the claims broadly encompass treatment of a wide range of conditions using a disparate group of bioactive molecules. The basis of the enablement rejection is that, given the unpredictability in the art, the teachings set forth in the specification are not applicable any condition or method of treatment other than those reduced to practice. Applicant is correct in asserting that enablement analysis concerns whether the disclosure enables a person of ordinary skill in the art to practice the claimed subject matter.

Given the breadth of the claimed subject matter, the disclosure clearly would not enable a person of ordinary skill to practice the invention in accordance with the full scope of the claims.

In response to the Examiner's assertion that it would be difficult to predict the brain weight of a human being, Applicant argues that the specification discloses exemplary dimensions of the human brain and thereby provides enabling data for predicting and/or determining the appropriate dose. This argument is persuasive to the extent that an appropriate dose can be correlated to brain size. However, given that the disclosure provides no correlation between effective dose and brain size for the vast majority of the claimed subject matter, the ability to estimate human brain size does not provide enablement for the full scope of the claimed subject matter.

Applicants further submit that they need not identify which route of administration is best; rather, the best mode of administration contemplated merely must be disclosed. Applicant's point is again taken to the extent that one of ordinary skill in the art would be able to identify an effective mode of administration without undue experimentation. However, the claims encompass subject matter that the art teaches is highly unpredictable, the unpredictability of which is not addressed in the instant disclosure. There is nothing in the disclosure to indicate that the teachings therein can be applied to the full range of conditions to be treated or modes of treatment encompassed by the claims.

Predictability and amount of experimentation:

In response to the Examiner's assertion that the disclosure in the specification does not predict success in humans, Applicant contends that predictability of success in humans is

irrelevant to the enablement analysis, while the prediction of the applicability of one teaching to another is the relevant test. Applicant argues that because the specification expressly teaches how to adjust the dosage from the rat to the human, the specification need not rely on the inherent predictability of the general field of endeavor of the claimed subject matter. This argument is not persuasive because Applicant has not provided an enabling disclosure for the full scope of the claimed subject matter, even in rats. Therefore, clearly the vast majority of the claimed subject matter, which is not enabled even in animal models, is not applicable to humans.

In response to the Examiner's assertion that the use of a rat model of stroke recovery is not an appropriate model for all the diseases covered by the claims. Applicant argues that, because claims 1-2 and 4-35 do not recite treatments of particular diseases, at issue in the enablement analysis is whether the specification adequately teaches a method of treating a subject with CNS damage or with brain damage, not whether the specification teaches how to treat a particular disease.

This argument is not found persuasive because, while it is true that the claims (other than claim 35) are not directed to treatment of a specific disease, CNS or brain damage encompass genera of widely divergent conditions (e.g., the conditions set forth in claim 35 and on page 12 of the specification). Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." Vaeck, 947 F.2d at 495, 20 USPQ2d at 1444; Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404; In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by

the specification). In the instant case, the disclosure clearly does not provide enablement for the full scope of a method of treating the genera of CNS or brain damage because there is no evidence that the method is effective in the treatment of the vast majority of species encompassed by either genus.

Finally, Applicant argues that the specification teaches that a wide variety of CNS and/or brain disorders can be treated using the disclosed methods (see page 12, paragraph beginning line 18), and that the literature cited by the Examiner emphasizes that similar approaches are often taken to treat CNS or brain damage, whatever its cause. This argument is not persuasive because the teachings of therapeutic stem cell transplantation in the disclosure and art at the time of filing are merely prophetic. Although stem cells could, in theory, be applied to treatment of a wide variety of conditions, as pointed out in the previous Office Action, the art at the time of filing was in its infancy. Park *et al.* teaches that many questions still need to be answered before the therapeutic potential of stem cells can be realized and that the goal, at the time of filing, should not be therapy but a better understanding of the biology (see Paper No. 18, page 9). These teachings indicate that at the time of filing treatment of any CNS or brain damage using the stem cell transplantation was far from routine. Therefore, practicing the claimed invention beyond the scope actually reduced to practice would require undue experimentation.

35 U.S.C. § 112, first paragraph, possession

In response to the Examiner's assertion that the specification fails to describe a representative number of the sequences encompassed by genus of polypeptides at least 30% identical to a bFGF polypeptide of SEQ ID NO:1, 2 or 3, Applicant argues that the disclosure

provides adequate evidence that the family of sequences encompassed by a polypeptide at least 30% identical to a bFGF polypeptide and their relatedness was known in the art at the time the application was filed. Applicant states, "no fewer than 9 factors being at least 30% identical to one of the disclosed sequences are disclosed and their general tertiary structure described" and "[t]he specification makes further reference to other members of the FGF family, also being at least 30% identical to one of the disclosed sequences" (Paper No. 19, page 13).

This argument has been fully considered but is not found persuasive because the claims are directed to a method of using a "a neural stimulant" having the structure of a polypeptides at least 30% identical to a bFGF polypeptide of SEQ ID NO:1, 2 or 3. As pointed out in the previous office action, "[i]n this case, since structure and/or function cannot be predicted from sequence, no identifying characteristics are provided for the claimed genus of sequences" (page 14). In other words, there is no evidence that the function of a neural stimulant useful in the claimed method is inherent to the structural limitations set forth in the claims. Therefore, Applicant has not set forth the relevant identifying characteristics of the genus of molecules encompassed by a bFGF polypeptide that is at least 30% identical to SEQ ID NO:1, 2 or 3 and with the function of a neural stimulant such that the skilled artisan would recognize that Applicant was in possession of the full scope of the claimed subject matter at the time of filing.

Claim Rejections - 35 USC § 103

In response to the rejection of claims 1,2 and 4-35 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Andsberg *et al.* in view of Alp *et al.* and in further view of Ip *et al.* and Daughaday et *al.* applicant traverses the rejection on several grounds.

First, Applicants note that the Examiner did not point out where in Ip a synergistic effect of using a combination in increasing the effectiveness of the neural stem cells is successfully demonstrated. Applicant is directed to the first full paragraph on page 16, in which Ip characterizes the combined effects of multiple factors on the growth and differentiation of neuronal precursors. Ip teaches, "these interactions do not result in simply the enhancement of the effect of one of the factors, but rather a differentiation process that is qualitatively much different from that resulting from treatment with any one factor alone". Applicant is also directed to the first paragraph on page 1, wherein Ip states, "[t]he present invention relates to a method of treating neuronal precursor cells to cause them to differentiate into neuronal-type cells. Such method is useful, e.g. to enhance the survival and functionality of cells used in striatal or other transplantation treatments". Thus, Ip teaches that the disclosed method provides improved growth and differentiation of neuronal precursors, which provides both a teaching of a method of treatment comprising administering a neurostimulant and motivation to combine this teaching with the other teachings cited.

Next, Applicant argues there no teaching in Ip of a method of administering to a subject stem cells and a neural stimulant wherein the conjoint administration of the stem cells and the neural stimulant ameliorates the effects of CNS damage. Ip does not describe how to perform the injection, routes of administration, the amounts of the components to inject, the dosage frequency, or other supporting disclosure that would enable one of ordinary skill in the art to perform the speculated method, or that would convey to one of ordinary skill that the inventors possessed their speculated method. While Applicant's characterization of the teachings of Ip are generally correct, this argument is not persuasive because the enabling disclosure is provided by

Andsberg *et al.* who teaches that grafted neural stem cells can ameliorate neuronal death in the adult rat striatum following ischemic injury. Thus, the method of Andsberg is already enabled for treatment of ischemic injury, and the skilled artisan would combine those teachings with the teachings of Ip merely to enhance differentiation of the neuronal precursor cells and improve the already enabled method. Likewise, with regard to claims 4 and 20, directed to neural stem cells, the teaching of neural stem cells is found in the primary reference (i.e., Andsberg *et al.*) and therefore need not come from Ip.

Thus, for reasons of record, the claimed invention as a whole would have been obvious to one of ordinary skill in the relevant art at the time the instant application was filed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
March 6, 2003

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER